



- 1 1. An isolated phosphorylated mammalian DARPP-32 protein comprising a
2 phosphorylated threonine residue; wherein the threonine residue can be reversibly
3 phosphorylated and dephosphorylated ; and wherein when the threonine residue is
4 dephosphorylated, it can be phosphorylated by Cdk5.
- 1 2. The phosphorylated mammalian DARPP-32 protein of Claim 1 which can
2 inhibit the kinase activity of cAMP-dependent protein kinase (PKA).
- 1 3. The phosphorylated mammalian DARPP-32 protein of Claim 2 wherein the
2 DARPP-32 protein has the amino acid sequence of SEQ ID NO:1 or SEQ ID NO:1
3 with a conservative amino acid substitution, and the threonine residue is the seventy-
4 fifth (75) amino acid residue of the amino acid sequence.
- 1 4. A phosphorylated fragment of a DARPP-32 protein, wherein the fragment of
2 the DARPP-32 protein comprises a phosphorylated threonine residue that when
3 dephosphorylated, can be phosphorylated by Cdk5.
- 1 5. The phosphorylated fragment of a DARPP-32 protein of Claim 4, wherein the
2 DARPP-32 protein has the amino acid sequence of SEQ ID NO:1 or SEQ ID NO:1
3 with a conservative amino acid substitution, and the threonine residue is the seventy-
4 fifth (75) amino acid residue of the amino acid sequence.
- 1 6. A fusion peptide comprising the phosphorylated fragment of a DARPP-32
2 protein of Claim 4.
- 1 7. A chimeric protein comprising the phosphorylated mammalian DARPP-32
2 protein of Claim 1.

- 1 8. A phosphorylation state-specific antibody having specificity for
2 Thr75-phosphorylated DARPP-32 having the amino acid sequence of SEQ ID NO:1.
- 1 9. The antibody of Claim 8 which is a monoclonal antibody.
- 1 10. The antibody of Claim 9 which is a chimeric antibody.
- 1 11. A method of identifying an agent that can modulate the phosphorylation state of
2 Thr75 DARPP-32 comprising:
 - 3 (a) contacting a potential agent with Cdk5 or an analog thereof, and
4 DARPP-32 or a Cdk5 phosphorylatable fragment of DARPP-32; and
 - 5 (b) determining the amount and/or rate of phosphorylation of DARPP-32 or
6 the Cdk5 phosphorylatable fragment of DARPP-32; wherein the potential agent is
7 identified as an agent that can modulate the phosphorylation state of Thr75 DARPP-32
8 if the amount and/or rate of phosphorylation of DARPP-32 or the Cdk5
9 phosphorylatable fragment of DARPP-32 determined is significantly changed in the
10 presence of the potential agent relative to in its absence.
- 1 12. The method of Claim 11 further comprising:
 - 2 (c) contacting the agent with an alternative protein kinase and a substrate
3 for that alternative kinase; wherein the alternative kinase is known not to
4 phosphorylate DARPP-32 on Threonine-75; and
 - 5 (d) determining the amount and/or rate of phosphorylation of the substrate;
6 wherein the agent is identified as an agent that can modulate the phosphorylation state
7 of Thr75 DARPP-32 if the amount and/or rate of phosphorylation of the substrate is
8 not significantly changed in the presence of the agent relative to in its absence.

1 13. The method of Claim 12 further comprising:

2 (e) administering the agent to a mouse along with a dopamine D1 receptor
3 agonist; wherein the administration of the dopamine D1 receptor agonist alone results
4 in an increase in the phosphorylation state of a cyclic-AMP dependent protein kinase
5 (PKA) substrate naturally occurring in the mouse; and

6 (f) determining the amount and/or rate of phosphorylation of the PKA
7 substrate; wherein the agent is identified when the amount and/or rate of
8 phosphorylation of the substrate is significantly decreased in the presence of the agent
9 relative to in its absence.

1 14. The method of Claim 13 wherein the agent can cross the blood brain barrier.

1 15. The method of Claim 14 further comprising:

2 (g) administering the agent to a DARPP-32 knockout mouse along with a
3 dopamine D1 receptor agonist; wherein the administration of the dopamine D1
4 receptor agonist alone results in an increase in the phosphorylation state of a cyclic-
5 AMP dependent protein kinase (PKA) substrate naturally occurring in the mouse; and

6 (h) determining the amount and/or rate of phosphorylation of the PKA
7 substrate; wherein the agent is identified when the amount and/or rate of
8 phosphorylation of the substrate is not significantly changed in the presence of the
9 agent relative to in its absence.

1 16. A method for treating dopamine dysregulation in an individual comprising
2 administering to the patient an agent that either inhibits the phosphorylation of
3 Thr75-DARPP-32 or promotes the dephosphorylation of Thr75-DARPP-32.

1 17. The method of Claim 16, wherein the dopamine dysregulation leads to a
2 symptom characteristic of a condition selected from the group consisting of
3 schizophrenia, Parkinson's Disease, Tourette's syndrome, Huntington's disease,
4 attention deficit hyperactivity and drug abuse.

- 1 18. The method of Claim 16, wherein the agent can cross the blood brain barrier.
- 1 19. The method of Claim 16 wherein the phosphorylation of Thr75-DARPP-32 is
2 inhibited by inhibiting Cdk5.
- 1 20. The method of Claim 19 wherein the agent is roscovitine.
- 1 21. The method of Claim 19 wherein the agent is a member of the class of
2 compound selected from the group consisting of an indirubin and a paullone.